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RESEARCH ARTICLE

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Intra-periaqueductal Grey Matter Injection of Orexin A Attenuates Nitroglycerin-induced Deficits in Learning and Memory in Male Rats

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ABSTRACT

This study explored the potential contribution of Orx1R within vlPAG to the learning and memory of animals with chronic migraine-like pain. Migraine was induced by repeated i.p. administration of nitroglycerin (5 mg/kg). Passive avoidance adeptness was evaluated in the shuttle box maze. The spatial memory performance was estimated using MWM tests. In the MWM task, NTG-injected rats revealed an imperative increase in escape latency and traveled the distance to catch the stage and a decrease in the time spent to pass into the goal zone in comparison to the control animals. Such NTG-evoked responses were attenuated by the post-treating intra-vlPAG injection of orexin A at 100 but not 25 and 50 pM. Furthermore, in the shuttle box test, NTG-treated rats showed eversion memory retrieval impairment as reflected by decreased phase through latency and longer time spent in the black chambers of the maze. Administration of orexin A at 50 and 100 pM could suppress NTG-related eversion memory deficiency in rats. However, orexin A (100 pM) aptitude to preserve memory performance, in both MWM and shuttle box tasks, was significantly prevented by SB334867 (20 nM) as an Orx1R antagonist. Overall, these data support the role of Orx1R within vlPAG to modulate migraine-related cognition deficits in rats.

Keywords

Migraine, Nitroglycerin, Orexin A, Learning and memory, Rats

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Abbreviations

PAG: periaqueductal grey matter
Orx1R: Orexin 1 receptors
vlPAG: ventrolateral periaqueductal grey matter
MWM: Morris water maze
CGRP: Calcitonin gene-related peptide
NTG: Nitroglycerin

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Introduction

Migraine is a pervasive brain complaint principally defined by unbearable pulsating pain in the head. In addition to headaches, people with migraine typically show some irregular expressions called aura as visual, sensory, or gastrointestinal problems [1, 2]. The management of migraine is multifaceted and migraine therapies annually impose a massive burden on the society and public health systems [3-6].

Migraine brains have structural and functional irregularities in the pain processing centers, including the trigeminocervical complex and PAG [7, 8]. It has been indicated that the functional association between PAG and some of the remaining nociceptive processing is altered in migraine patients [7]. In particular, axon terminals from PAG have been traced in trigeminal sensory nuclei through neurons in the nucleus raphe magnus [9]. In addition, the activation of PAG neurons modulates the spinal trigeminal neurons in a cat model of trigeminovascular pain [10]. During migraine attacks, the irregular activation of trigeminal afferent neurons innervating cerebral blood vessels could induce cerebral vasodilation by releasing vasoactive peptides, such as CGRP and substance P, which may have a role in pain sensitization [11-14].

It has been demonstrated that normal cognitive processing is disrupted in migraine. Although most studies display an elevated risk of cognitive dysfunction in migraine patients, there are some paradoxical data. For example, it has been indicated that migraine induces significant deficits in visual attention and verbal memory [15-17]. However, in the study by Jelicic et al., migraine did not alter cognitive performance in middle-aged or older adults [18]. Moreover, long-lasting migraine headache in middle-aged twins was not accompanied by cognitive dysfunction [19]. A familial hemiplegic migraine mutation inspired significant spatial memory deficiency in contextual fear-conditioning and MWM tests in mice. It could also increase hippocampal excitatory transmission and long-term potentiation [20].

The orexin peptides (A and B) are expressed by different neurons in the hypothalamus. These peptides stimulate distinct G protein-coupling receptors, Orx1R and Orx1R [21, 22]. Distributed cortically and subcortically, orexinergic neurons are involved in nociceptive transmission [23-25]. The manipulation of Orx1R has been shown to alter migraine headache intensity. Intravenous infusion of orexin A might modulate nociceptive neurons to trigeminal nucleus caudalis in rats the model of dural trigeminovascular nociception [26].

It is well documented that Orx1R plays a vital role in learning and memory processing. Activation of Orx1R in the hippocampus improved spatial learning and LTP in rats [27, 28]. In addition, trigeminal pain-associated learning and memory deficits in rats were suppressed by orexin A injection in the trigeminal nucleus caudalis or rostral ventromedial medulla of rats [29, 30]. Moreover, the blockade of orexins receptors in the basolateral amygdala could disturb the passive evasion memory of rats [31].

There are functional connections between PAG circuits mainly vlPAG with cortical and subcortical brain regions in either pain or learning and memory processing, including the thalamus, prefrontal cortex, insular agranular, and amygdala [32-34]. Therefore, the current study aimed to show if manipulating Orx1R in vlPAG could alter the learning and memory values of rats with migraine headaches.

Abbreviations-Cont'd

MAPK: Mitogen-activated protein kinase
ANOVA: One-way analysis of variance
NO: Nitric oxide
ERK: Extracellular signal-regulated kinase
CB1R: Cannabinoid 1 receptors

Results

MWM

During acquisition blocks, the groups showed significant alterations in latency scores to find the concealed platform [F (3, 483)=33.634, $p = 0.001$]. Post hoc comparisons indicated that NTG administration could significantly increase latency time to catch the platform in the first, third, and fourth blocks of acquisition trials ($p < 0.05$) (Figure 1). Nevertheless, post-training administration of orexin A (100 pM) attenuated latency time in all blocks. In addition, orexin A at 50 pM could decrease escape latency to the platform in the third and fourth blocks compared to the NTG group ($p < 0.05$) (Figure 1). However, orexin A (100 pM) was inhibited by prior treatment infusion of SB334867 (20 nM) (Figure 1).

Moreover, our results indicated a significant differences between groups in the space traveled to find the concealed platform during the acquisition test [F (3, 483)=28.626, $p = 0.001$]. As shown in Figure 2, the distance traveled to find the stage significantly increased in NTG or NTG plus normal saline-treated groups in all acquisition trials. Orexin A administration at 100 pM but not 25 and 50 pM could repress NTG-increased moved distance to catch the stage ($p < 0.05$) (Figure 1). Such effects of orexin A (100 pM) were disallowed by SB334867 (20 nM) (Figure 2).

In the probe trial, the groups showed a significant difference in the time spent [F (6, 41)=8.061, $p = 0.001$] and the number of visits [F (6, 41)=6.408, $p = 0.001$] across the target area. As shown in Figure 3, the total number of visits and time spent in the goal region significantly attenuated in NTG-treated rats. Orexin A administration at 100 pM but not 25 and 50 pM augmented the number of visits and the time spent in the goal zone compared to the NTG groups ($p < 0.01$ and $p < 0.05$). However, orexin A (100 pM) value to increase the number of visits and the time spent in the goal region was inhibited by pre-treatment administration of SB334867.

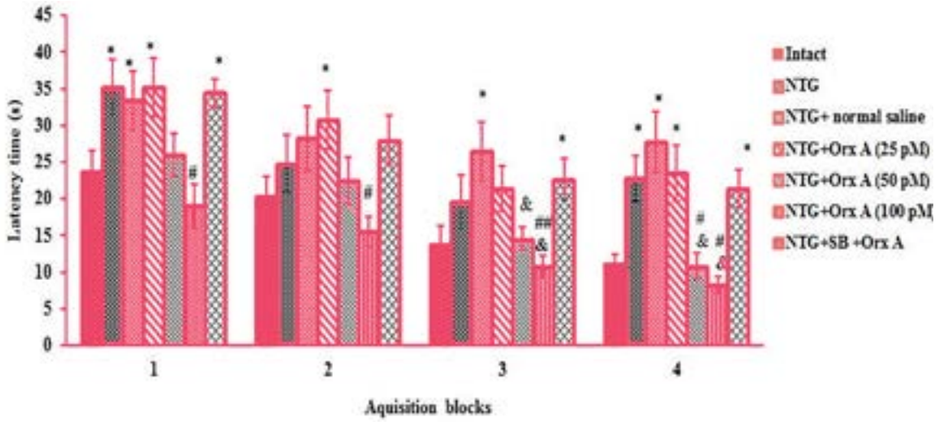

Figure 1.
Comparison rats escape latency during acquisition blocks to reach the hidden platform in MWM test between groups. $^{*}P < 0.05$ vs intact, $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ vs NTG- treated group, $^{\&}P < 0.05$ vs NTG + normal saline group. NTG: nitroglycerin; SB: SB334867; Orx A: orexin A.

Figure 2.
Comparison distance travelled by rats to reach the hidden platform during acquisition blocks of MWM test between groups. $^{**}P < 0.01$, $^{*}P < 0.05$ vs intact, $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ vs NTG- treated group, $^{\&\&}P < 0.01$, $^{\&}P < 0.05$ vs NTG + normal saline group. NTG: nitroglycerin; SB: SB334867; Orx A: orexin A.

Shuttle box

Assessment of passive avoidance memory retrieval in the shuttle box test showed a significant difference between groups in phase through latency and time spent in a dark hall. Post hoc test showed decreased step through latency ($p < 0.05$) and increased time spent in the darkroom ($p < 0.01$) in rats infused by NTG or NTG+ vehicle in comparison to untreated control rats. The NTG-induced reduction in step-through latency ($p < 0.05$) and the rise in the time spent in the dark chamber were attenuated with orexin A (50 and 100 pM). However, orexin A (100 pM) amended effects on memory retrieval prevented by the co-injection of SB334867 (20 nM) (Figure 4).

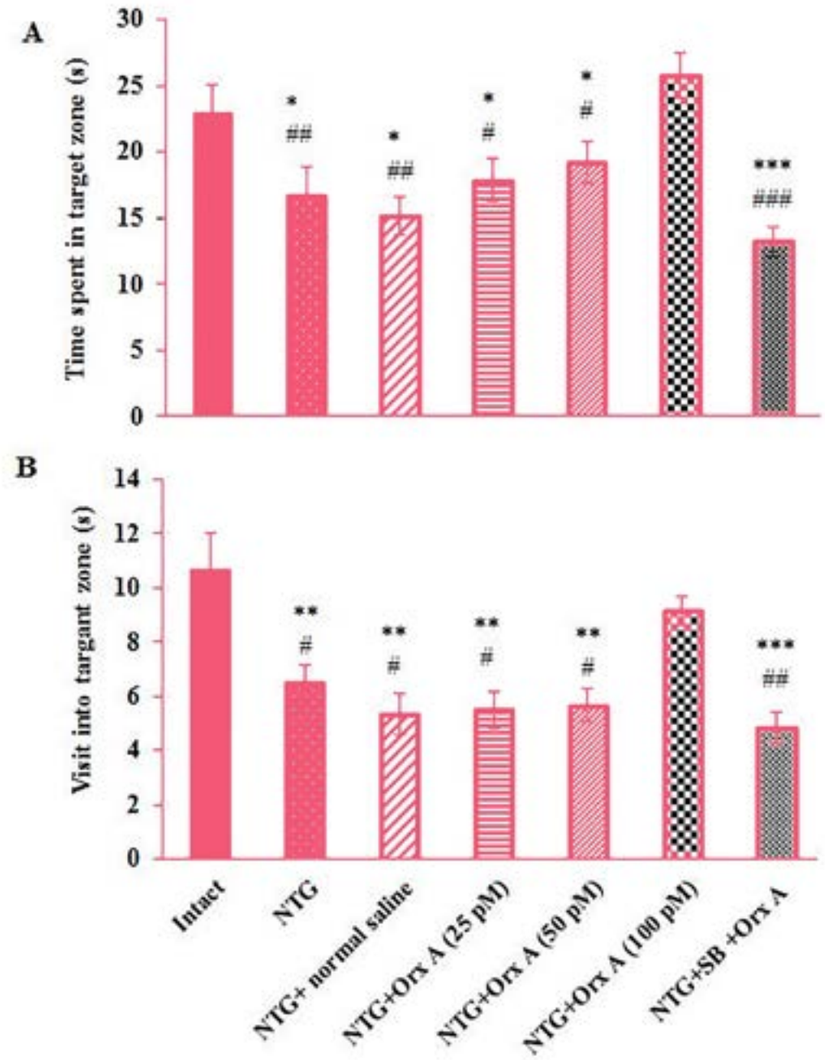

Figure 3.
Comparisons the time spent (A) and the numbers of visit (B) into goal zone among experimental groups. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ vs intact, $^{\#\#\#}P < 0.001$, $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ vs NTG+Orx A (100 pM) treated group. NTG: nitroglycerin; SB: SB334867; Orx A: orexin A.

Discussion

This study investigated the influence of the post-treatment infusion of orexin A in vlPAG on learning and memory competence in a rat model of NTG-evoked migraine. According to our results, orexin A dose-dependently improved learning and memory indices in rats exposed to migraine. The effects of orexin A were suppressed by the prior injection of Orx1R antagonist SB334867.

Migraine headaches have been shown to interfere with normal cognitive processing in the brain [20, 35]. In this study, the systemic administration of NTG induced severe memory impairments. Consistent with our findings, it has been indicated that NTG-reduced vasodilation disturbs passive avoidance memory performance in mice [36]. The NTG, as a donor of NO, plays a vital role in regulating physiological functions under normal conditions [37, 38]. However, irregularly increased NO levels in the hippocampus disrupted cognitive processing in hypothyroid rats [39]. Furthermore, diminished NO is associated with a reduction in age-associated cognitive deficits in NO

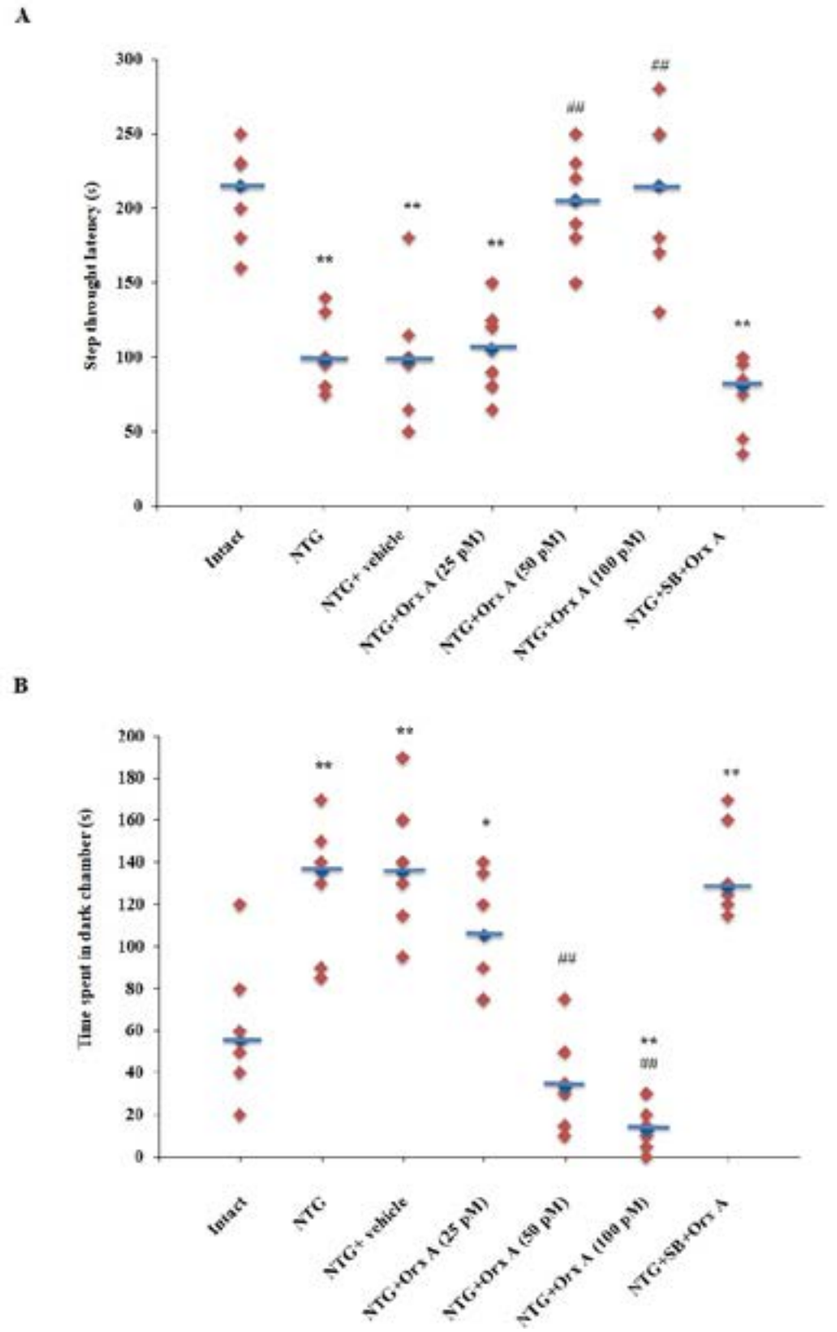

Figure 4.
Comparisons step through latency (A) and time spent in dark chamber (B) in shuttle box test among experimental groups. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ vs intact, $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ vs NTG+Orx A (100 pM) treated group. NTG: nitroglycerin; SB: SB334867; Orx A: orexin A.

synthase mutant mice [40]. These studies support the idea that NTG administration could induce learning and memory deficits by changing the synthesis or release of NO in the brain.

Here, for the first time, we demonstrated that the pharmacological stimulation of Orx1R in vlPAG decreased learning and memory disruption in migraine model rats. Previous studies have strongly specified that the orexinergic system within vlPAG is involved in the transmission of nociceptive signals, such as trigeminal nociception [41, 42]. Orexin A analgesic activity is accompanied by ameliorating cognitive deficiency in rats. Notably, Orx1R stimulation in the trigeminal nucleus caudalis and restroventral medulla could reduce learning and memory deficiency persuaded by dental inflammation in rats [29, 30]. In addition, it has been indicated that orofacial pain-induced memory disruption is associated with reductions in Orx1R concentration in the hippocampus of rats [43]. Consequently, this study shows that orexin A competence against NTG-induced learning and memory deficiency might be related to the modulation of migraine pain transmission in the vlPAG circuits [41].

Many signaling pathways are triggered by orexin A especially classical ERK/MAPK, and cAMP-PKA cascades in the brain [44]. Noticeably, central infusion of Orx1R agonist suppressed learning and memory deficits in pentylenetetrazol-kindled rats via activating Orx1R and ERK1/2 pathways [45]. In addition, the perifornical hypothalamus and central amygdala orexinergic neurons are involved in the modulation of conditioned fear memory through activating phospholipase C and sodium-calcium exchanger pathways in rats [46]. Moreover, orexin A declined cognitive lack and upregulated BDNF expression in a rat model of Parkinson's disease by inducing phosphatidylinositol 3-kinase and PKC signaling [47]. As a hypothesis, the influence of orexin A efficiency on learning and memory might be partially achieved by intracellular molecules driven by Orx1R activation. Nevertheless, further studies are needed to display the careful mechanism(s) behind such a phenomenon.

The PAG is a nonspecific place for controlling the learning and memory process. However, PAG circuits make direct or indirect influences on the brain areas complicated in-memory processing, including thalamic nuclei, hypothalamus, amygdala, and lateral prefrontal cortex [48, 49]. Functional connectivity has been reported between PAG and prefrontal cortex, CA1 area of the hippocampus as well as amygdala during the formation of contextual fear conditioning memory [50]. In addition, axonal projection from the prefrontal cortex to vlPAG is involved in contextual fear discrimination and generalization [51]. The current study showed that the activation of excitatory Orx1R signaling within vlPAG can manipulate vlPAG afferents to cortical areas involved in the control of learning and memory.

In the vlPAG, orexinergic neurons are found with the neuronal subpopulations that express a variety of neuro-regulatory molecules, such as glutamate, GABA, and cannabinoid [41, 52-55]. It has been indicated that association between Orx1R and CB1R in vlPAG may induce analgesic effects by modulating GABAergic and glutamatergic neurons [41]. In addition, the pharmacological blockage of either Orx1R or CB1R within vlPAG blocked the carbachol-induced antinociception in rats [56]. Furthermore, intranasal orexin A administration raised glutamate flow in the cortex [57]. Consequently, it is hypothesized that Orx1R crosstalk with other receptor systems within PAG could alter subjective behavior as previously reported for nociception in rats.

Conclusion

In conclusion, the results of this study showed that Orx1R in vlPAG is involved in the modulation of learning and memory deficiency induced by the NTG model of migraine headaches in rats. These findings support the potential efficiency of Orx1R medicine in controlling cognitive deficiency comorbid with migraine headaches.

Animals

Adult male Wistar rats were used. The rats were preserved on a 12 h light/dark typical cycle at a specific temperature of 22°C ± 2°C. The rats had ad libitum access to food and water. The experimental processes were certified by Shahid Bahonar University Animal Care and Ethics Committee (IR.UK.VETMED.REC. 1398.003).

Surgical procedure

The rats were anesthetized by ketamine and xylazine solvation (60 and 5 mg/kg/ i.p., respectively) and were sited on a stereotactic device. A hole was punctured in the skull and a stainless steel guide cannula was fixed in vlPAG at stereotaxic coordinates AP: 7.8, LM: 0.6, and DV: 5.9 mm [58]. All the rats were endorsed one week postoperative prior to the start of the tests. At the end of the process, the precise location of the cannula for each rat was certified histologically (Figure 5).

Medications and microinjection

Nitroglycerin was purchased from Caspian Tamin, Rasht, Iran. Orexin A and SB334867 (both Sigma, USA) were liquefied in saline and dimethylsulfoxide, respectively. The medications were infused into vlPAG by an injector needle (30 g) attached to a polyethylene pipe to a 1 µL Hamilton syringe. All medicines were dispersed over 1 min. The needle was left in the site for an additional 60 sec to block backflow and consent medicine distribution.

Experimental design

Chronic migraine pain was prompted by the i.p. administration of NTG (5 mg/kg) (five injections in total). Next, the animals were arbitrarily distributed into different experiment groups as follows: intact (control), vehicle, orexin A (25, 50, 100 pM), and SB 334868 (20 nM)+orexin A (100 pM). Animals in the vehicle and orexin A groups were infused with the intra-vlPAG administration of normal saline or orexin A (25, 50, 100 pM). The SB 334868 (20 nM)+orexin A (100 pM) group received SB 336747(20 nM) followed by orexin A (100 pM).

Evaluation of learning and memory

MWM test

The MWM contained a dark spherical pool (136 cm in diameter and 60 cm in height). The additional indications were positioned in defined sites on the room test walls which were detectable to the animals. The pool contained water (22°C±1°C) to a depth of 25 cm alienated into four distinct zones by four main instructions. A spherical stage was situated in the middle of one of the zones (2 cm below the water outward). First, each animal was placed in the water from one of the directions. The animal movement was shadowed by a numeral camera fixed above the central area of the pool and was measured using the Ethovision software.

The experiment included learning and probe assessments. The learning test was accomplished on three successive days (four trials per day). The rats were indorsed to swim within the maze to hook the covered stage. When the stage was perceived, the animal had to remain on the stage for 30 sec. The time of escape latency and moved space by each animal were appraised. In the memory test, one day after the learning test, the covered stage was detached from the pool. Afterwards, animals were located in the quadrant as opposed to the goal quadrant and were indorsed to swim for 1 min. The visit to the goal zone and the time spent were noted.

Shuttle box test

The apparatus consisted of two distinctive halls (light and dark). There was a plexiglass door between two halls. The learning experiment comprised acclimatization and achievement trials. In the acclimatization examination, the rats were separately sited in the light hall and permitted to go in the black hall. In the acquisition experiment, each rat was positioned in the bright room, and the behead door was undone. When the rats entered the dim hall, the gate was barred and a persistent electric shock was exerted via the gridiron floor. In case the animal did not arrive in the dark area in 5 min, the success of learning was deliberated effectually. The total number of learning trials was calculated. After one day, in the maintenance trial, the rats were positioned in the light room and indorsed to onset into the dark box. Phase through latency and the time expended in the darkroom were noted for each rat. The maximum cut-off time was set up at 5 min.

Statistical analysis

The data of the MWM test (learning trials) were analyzed by repeated measures ANOVA. Furthermore, the results of the probe trial were assessed using one-way ANOVA. Differences between groups were analyzed by Tukey's post hoc test. In the shuttle box task, the data were analyzed with Kruskal–Wallis H test. In addition, multiple comparisons were performed utilizing the Mann-Whitney-U test. *P*-values less than 0.05 were considered imperative.

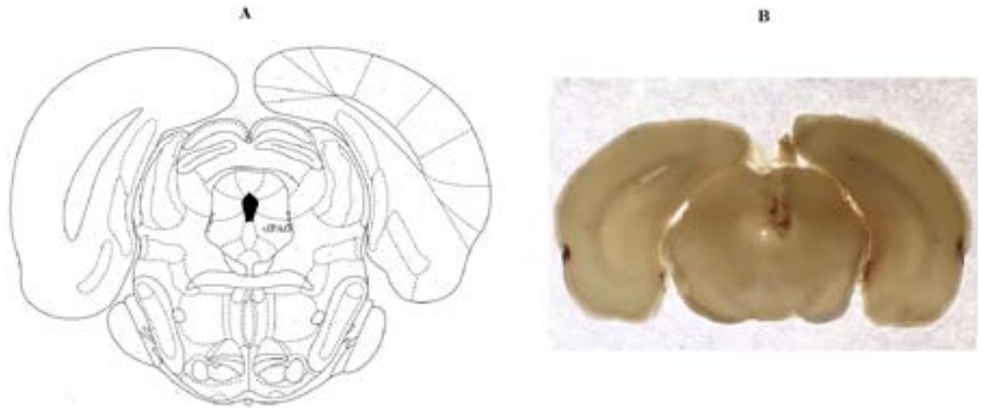

Figure 5.
A representative vlPAG section replicated from rat brain atlas of Paxinos and Watson (A) and a illustrative brain coronal section displaying the injection place (B).

Authors' Contributions

RK intended the experiments, performed the procedures, and analyzed the data. MA supervised the study and drafted the manuscript.

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Competing Interests

The authors declare that they have no conflict of interest according to the work presented in this report.

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